TETRACYCLINES IN RENAL INSUFFICIENCY: RESOLUTION OF A THERAPEUTIC DILEMMA *

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PATIENTS with acute or chronic renal failure are at a particularly high risk of development of bacterial infections.[1] During the 1960s and 1970s we have witnessed what amounts to a totally new era in the management of such renal failure patients. The widespread clinical use of chronic maintenance dialysis for individuals with chronic renal failure and our better understanding of the pathophysiology of acute and chronic renal failure have greatly increased the number of such patients under the care of medical or surgical practitioners. Virtually all drugs are eliminated in part or wholly from the body by renal excretion. Hence, patients with either mild or severe renal disease have become the focus of intense investigation defining the alterations that such renal impairment induced in the pharmacokinetics of drugs used in their medical and surgical management.[2-4] Because patients with kidney disease are particularly at risk of bacterial infections, it is not surprising that antibiotic drugs have received particular attention.

This review will reevaluate the use of tetracycline drugs in patients with renal disease. It will identify some of the important recent investigations that have contrasted what we might call the "old" tetracyclines such as chlortetracycline, oxytetracycline, or tetracycline hydrochloride with the "new" tetracyclines such as doxycycline and minocycline with respect to their use in bacterial infections complicating renal disease. It has often

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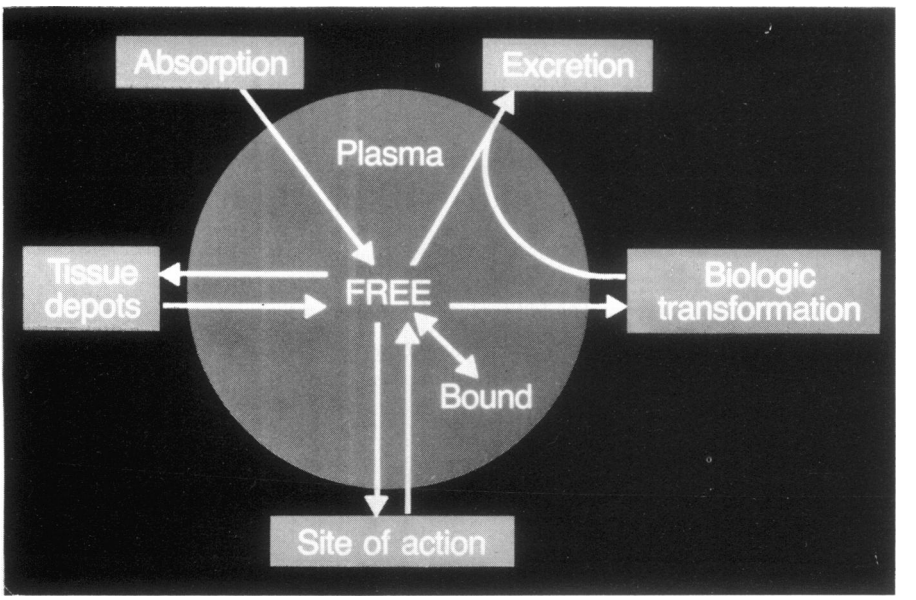

Fig. 1. Schematic representation of the fate of an antibiotic following oral or parenteral administration. Reproduced with permission from Whelton, A.: Antibacterial chemotherapy in renal insufficiency: A review. *Antibiot. Chemother. 18*:1, 1974.

been stated that the tetracyclines should be avoided in patients with severe renal disease, but, as we shall see, doxycycline represents an important exception to such a rule.

To understand why most tetracyclines, with the notable exception of doxycycline, manifest a systemic toxic accumulation if given either to patients with severe progressive renal disease or to those already maintained by chronic dialysis, we should briefly review the mechanisms by which the healthy individual eliminates drugs from the systemic circulation.

PHARMACOKINETICS

Following administration of an antibiotic chemotherapeutic compound by the oral or parenteral route, it initially circulates in the bloodstream either in a free state or bound to plasma proteins. A general schema of what happens to an antibiotic following absorption is depicted in Figure 1. The efficacy of the drug is related to the local concentration and ease with which it reaches its site of action—in this instance the interior of an

infecting bacterium. The drug concentration at the infecting site and the ease with which it reaches the site of action are correlated with all of the following: the rate of absorption of the drug, its distribution through the body compartments, the degree of serum protein and tissue binding, the rapidity of biotransformation or degradation in the liver or peripheral tissues, and, finally, the rate of excretion from the body. As a general rule, the therapeutic effectiveness or potential systemic toxicity of an antibiotic is directly related to its serum concentration, thus allowing one easy access to a means to follow or to predict therapeutic response to antibiotics or to alert one to the potential development of systemic toxicity secondary to antibiotic administration.

Duration of the effectiveness of action of an antibiotic is related to the rate with which the compound is absorbed into the systemic circulation from the site of administration and to the rapidity with which it is removed from the bloodstream. For each antibiotic compound a healthy individual demonstrates a relatively constant rate of absorption of the drug into the bloodstream and a separate but similarly constant elimination rate of the drug from the blood. This latter elimination rate is clinically designated as the serum half-life (T½) of the antibiotic and is mainly related to the degree of plasma protein binding of the drug and the rate of liver metabolism of the compound. For example, oxytetracycline, which is metabolized to a minor extent in the liver and is only 10 to 15% plasma protein bound, has a serum T½ of eight to nine hours, while doxycycline, not metabolized to any clinically important extent by the liver and 85 to 95% plasma protein bound, has a serum T½ of 20 to 24 hours.[2,5,6] Hence, in clinical usage it would be necessary to administer a compound such as oxytetracycline three times a day, while doxycycline, because of its prolonged serum T½, would have the distinct advantage of once-daily administration.

The prolonged serum T½, extensive plasma protein binding, and remarkable degree of lipophilicity, or lipid solubility, are the physical chemical properties that place doxycycline and minocycline in a separate pharmacologic niche from the "old" tetracyclines.

Renal Excretion

A summary of the renal excretion of tetracyclines is presented in Figure 2. We shall evaluate separately the contribution of the renal glomerulus, proximal tubule, and distal collecting duct to the overall renal elimination of tetracyclines.

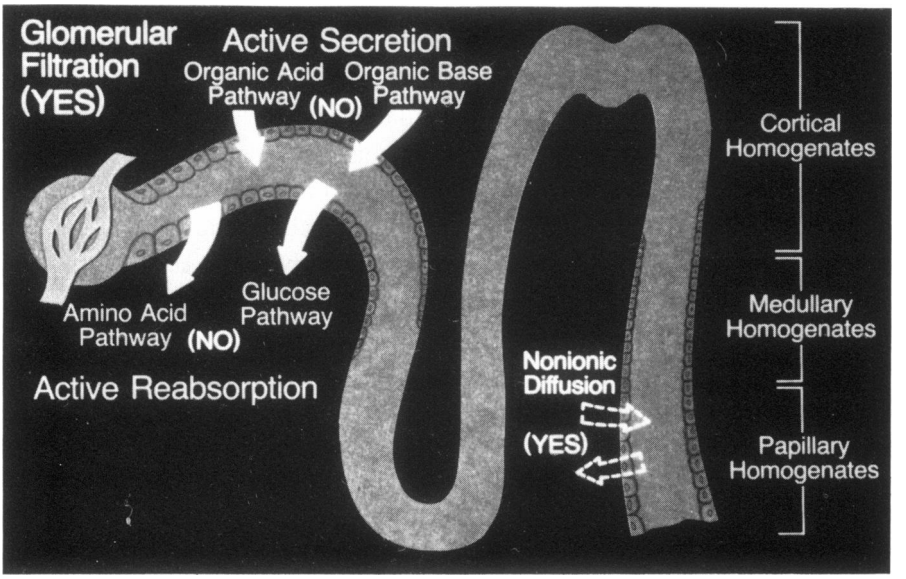

Fig. 2. Modalities of renal excretion of the tetracyclines in different locations of the nephron.

Glomerulus. Tetracyclines are filtered through the renal glomerulus by a purely mechanical hydrostatic phenomenon. The rate of filtration is directly related to the degree of plasma protein binding of these compounds because only the "free" drug can be filtered through the basement membranes of the capillaries in the glomerulus. From the plasma protein binding figures previously mentioned one could anticipate the clinical finding that oxytetracycline (15% protein bound) has a high rate of glomerular elimination, while doxycycline (85 to 90% protein bound) has a low rate of glomerular clearance, which therefore contributes to its prolonged plasma T½. In normal individuals oxytetracycline is almost entirely eliminated from the body by renal glomerular filtration, but, by contrast, only 50% of doxycycline is eliminated by the kidney, whereas the remaining 50% is eliminated by the gastrointestinal tract. This latter route of elimination is of paramount importance in patients with severe renal disease, as will be described later.

Proximal tubule. The cells of the proximal renal tubule can actively transport drugs into or reabsorb them from the lumen of the tubule. Active secretion of a drug from blood in the peritubular capillary complex through the organic acid or organic base transport systems into the lumen of the

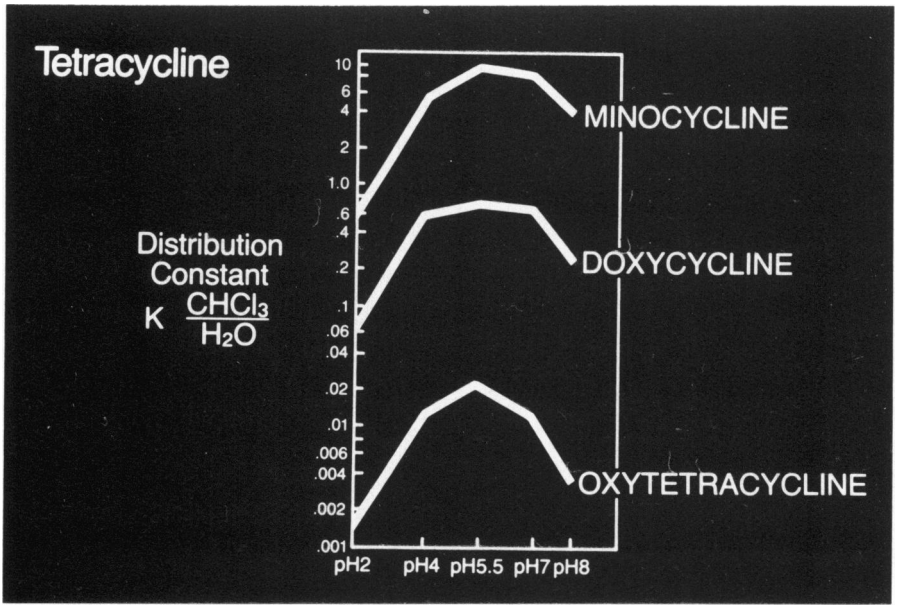

Fig. 3. Lipophilicity (solubility in $CHCl_3/H_2O$) of the "new" tetracyclines (doxycycline and minocycline) versus the "old" ones (for example, oxytetracycline). Data extrapolated from text reference No. 11. Reproduced with permission from Schach von Wittenau, M. and Yeary, R.: The excretion and distribution in body fluids of tetracyclines after intravenous administration to dogs. *J. Pharmacol. Exp. Ther. 140*:258, 1963.

tubule is by far the most important renal tubular mechanism for drug elimination from the body.[7,8] In the case of the tetracyclines, there is no solid evidence that secretory or reabsorptive mechanisms contribute in an important clinical fashion to their renal elimination.

Collecting duct. The final portion of the tubule that might possibly modulate the renal excretory rate of the tetracyclines is the collecting duct. It is within this location of the nephron that the final *p*H of the urine is produced, and the tubule can produce urine from an acid *p*H to an alkaline *p*H, ranging from 4.5 to 8.5 in normal individuals.

Most antibiotics are derivatives of either weak acids or weak bases. This means that in an alkaline solution (i.e., alkaline urine) an acid antibiotic dissociates or becomes ionized. In this ionized fashion, the antibiotic molecule now possesses an electric charge, and in such a charged state cannot easily pass through a biologic barrier such as the lining epithelium of the renal collecting duct.[7-9] Hence, in an alkaline urine an acid drug derivative such as acetylsalicylic acid becomes ionized, is not reabsorbed,

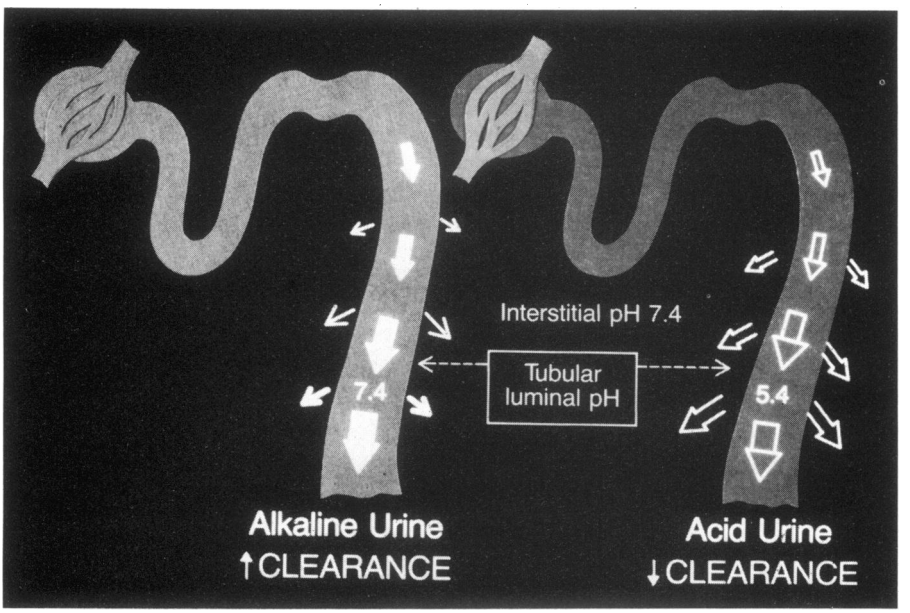

Fig. 4. Influence of urine *p*H upon the distal tubular nonionic diffusion of doxycycline.

and, accordingly, is eliminated in the urine. This is a matter of clinical importance, for example, in the management of acetylsalicylic acid poisoning. In the case of the tetracyclines, there is no evidence that the "old" drugs are influenced in their renal elimination rate by adjustment of urine *p*H. Doxycycline is an important exception.

The collecting duct traverses the renal medulla and papilla, and it is in these anatomic locations that the renal tissues demonstrate a particular susceptibility to bacterial infection.[10] We therefore questioned that possibly, given the appropriate physical chemical structure of an antibiotic, the urine *p*H might be manipulated so that the drug's movement from or retention within the lumen of the collecting duct could be scientifically predicted. In essence, we would have, for example, the situation of an acid antibiotic in an acid urine with a resulting decrease in ionization of the drug and diffusion of the compound from the collecting duct lumen into the potentially infected interstitium of the renal medulla and papilla.

Doxycycline is an excellent drug for investigation of urine *p*H influences upon renal excretion and tissue-drug concentrations. Although a zwitterion (i.e., possesses acidic and basic properties), its maximum lipid solubility (Figure 3), and hence diffusibility, occurs at *p*H 5.5.[11] This

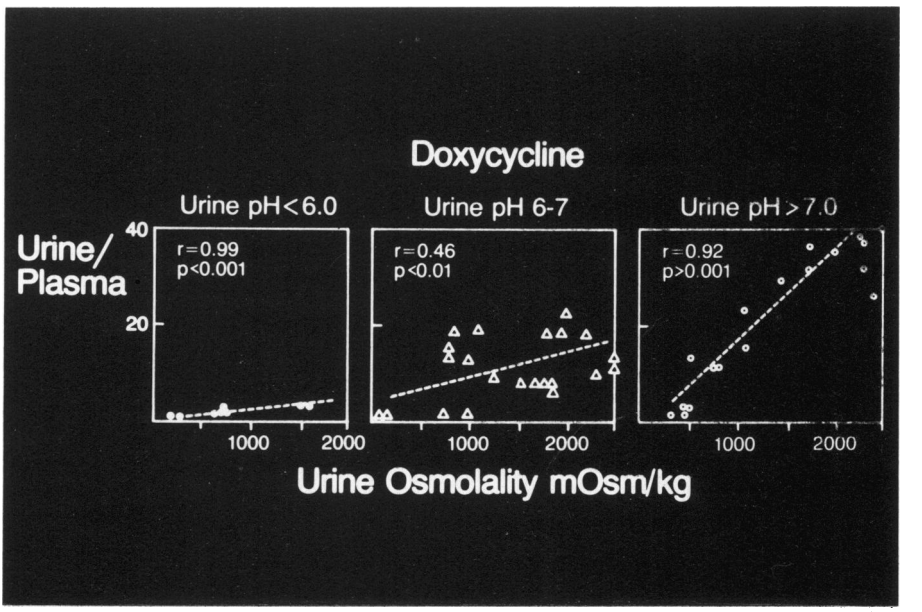

Fig. 5. Urine *p*H and osmolality influence upon doxycycline renal excretion. Alkaline urine enhances renal excretion.

means that maximum diffusibility of the drug across the lining of the collecting duct into the renal interstitium would occur during the production of acid urine. On the other hand, maximum ionization and trapping of the drug within the collecting duct lumen would occur in alkaline urine such that we would find enhanced renal clearances and urine concentrations of the drug in such physiologic circumstances.

Figure 4 is a diagram of what we found experimentally when we adjusted urine *p*H values during the excretion of doxycycline in a healthy dog model.[12] We found (Figure 5) an average fourfold increase in renal drug clearance when urine *p*H was changed from acid (*p*H 5 to 6) to alkaline (*p*H 7.0 to 8.0); however, in terms of clinical impact, the quantity of drug shunted into or removed from the medullary and papillary interstitium was not sufficient to change the tissue homogenate concentration of the drug measurably.[12] Thus far, no prospective clinical trials have been undertaken to identify whether the *p*H-induced modulation of renal doxycycline excretion is of any importance. Nevertheless, the animal investigations described give some useful predictive information that allows one to correlate a drug's physical chemistry and what can be predicted about its renal excretory characteristics.

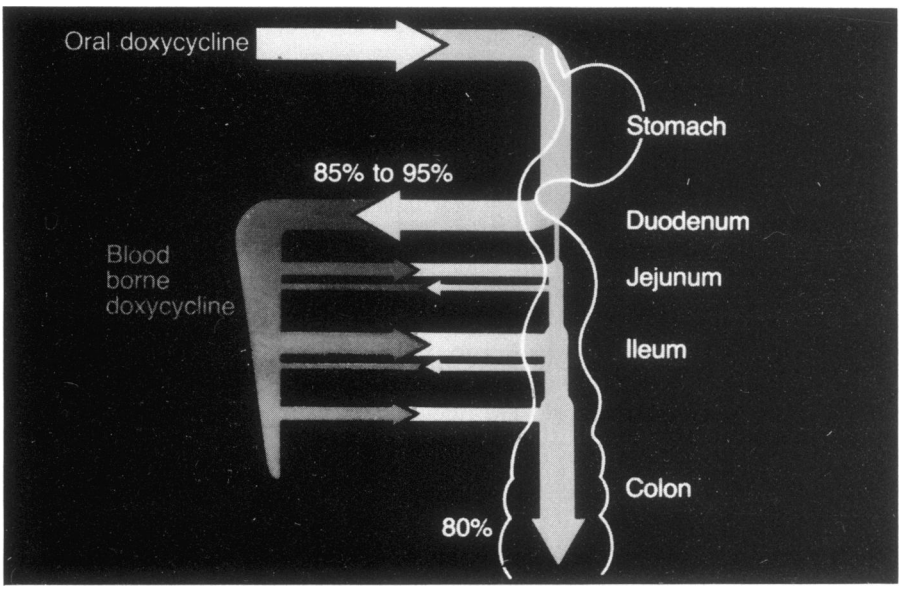

Fig. 6. Pharmacokinetic characteristics of doxycycline in the intestinal tracts of humans with severe renal insufficiency. Eighty percent or more is eliminated by the gut, and the remainder is removed in large part by hemodialysis. Reproduced with permission from Whelton, A., Schach von Wittenau, M., Twomey, T. M., Walker, W. G., and Bianchine, J. R.: Doxycycline pharmacokinetics in the absence of renal function. *Kidney Int.* 5:365, 1974.

Excretion by the Gastrointestinal Tract

Investigations performed outside the United States, where doxycycline had been clinically available for a longer time, first stimulated our interest in the excretion of doxycycline in patients with severe renal impairment.[13-16] These studies indicated that doxycycline was quite distinct from the "old" tetracyclines and from minocycline[17] because it neither accumulated systemically nor caused toxicity in patients with renal disease.

To resolve the clinical question concerning nonaccumulation of doxycycline in the absence of renal function, we concentrated our attention on the gastrointestinal excretory characteristics of the drug because animal models indicated that excretion of unchanged drug into the bowel was a major route of doxycycline elimination.[5,18] We administered tritiated doxycycline to a group of patients who were anephric and were maintained by hemodialysis while awaiting renal transplantation. Figure 6 summarizes our findings and indentifies the "alternate" route of doxycycline excretion in renal impairment. Following oral administration, the drug is highly

ionized in the *p*H 1 to 2 contents of the stomach. High concentrations of free drug are then introduced into the duodenum, where the *p*H is converted to the alkaline range, with the result that doxycycline between *p*H 5 and 6 becomes maximally lipid soluble and is absorbed essentially completely into the bloodstream. Parenthetically, this is in contradistinction to the "old" tetracyclines, where only 50% of the drug is absorbed as the remainder is directly introduced into the large bowel, which causes well-known problems from change in the intestinal bacterial flora. Blood-borne doxycycline reaches all parts of the body and, in addition, is presented to the serosal surface of the small and large bowel. Diffusion into the intestinal lumen takes place. In the alkaline milieu of the small and large bowel, cationic chelation occurs (i.e., binding of doxycycline to the high concentrations of calcium or magnesium contained in the bowel lumen), and in this chelated form doxycycline cannot be reabsorbed and loses most of its antibacterial properties. Hence, it does not change the bowel flora. The capacity of the intraluminal contents to bind successive amounts of doxycycline is not readily superseded because daily doses of the drug are small, and new intraluminal contents are constantly added to the small bowel by gastric emptying and biliary, pancreatic, and succus entericus secretions. Minor additional contributions to fecal elimination of the drug are made by biliary secretion.

Thus, absorption followed by transmucosal diffusion and intraluminal chelation of the compound so that it cannot be reabsorbed seems to be the mechanism that resolves the somewhat contradictory facts of sequential upper intestinal absorption followed by small and large bowel excretion. These investigations, then, clarify the nonrenal, nonhepatic. gastrointestinal "alternate" pathway for doxycycline elimination in patients with significant renal impairment. Our human studies[6] have also identified that the removal rate of the drug by hemodialysis is not of clinical significance. Doxycycline appears to be unique, therefore, among the tetracyclines in that when renal failure complicates clinical management decisions, or indeed when the renal functional status is not known, doxycycline is the drug of choice if a tetracycline is indicated for a systemic infection.

Metabolic Disorders Induced by Tetracyclines

The mode of antibacterial action of the tetracyclines is inhibition of amino acid incorporation into protein synthesis. This key antianabolic effect, first noted by Bateman and colleagues,[19] becomes manifest when

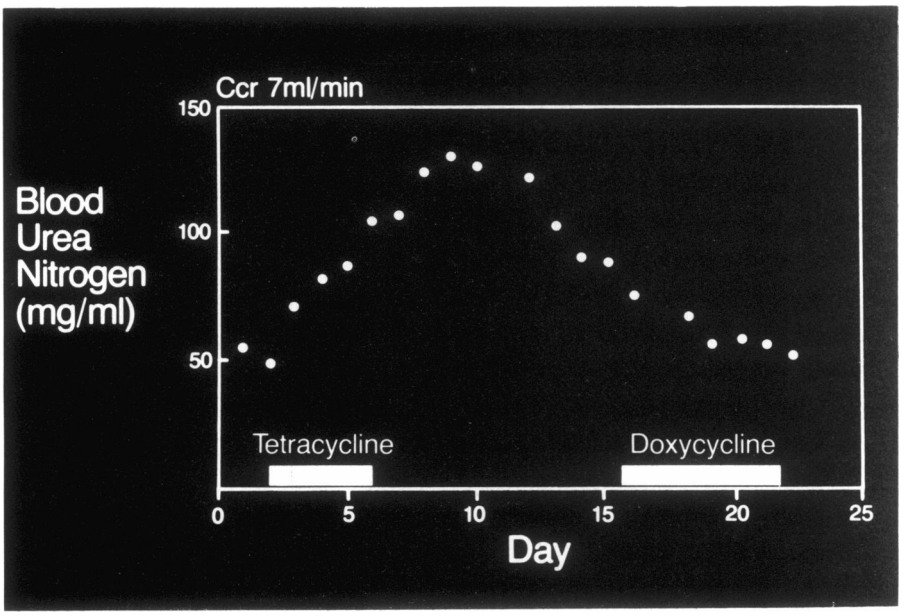

Fig. 7. Influence of tetracycline hydrochloride versus doxycyline upon the blood urea nitrogen values of a patient with significant renal disease. Data extrapolated from text reference No. 23. Reproduced with permission from Little, P. J. and Bailey, R. R.: Tetracyclines and renal failure. *N. Z. Med. J.* 72:183, 1970.

the tetracyclines are used in patients with compromised renal function. In such patients the usual serum T½ of the "old" tetracyclines (except chlortetracycline, which has a high rate of liver metabolism) may increase from eight to 10 hours to as much as 100 hours. As a result, the decreased utilization of amino acids in protein synthesis leads to the systemic accumulation of nitrogenous products in excess of the excretory capacity of the diseased kidney.[20] Metabolic abnormalities are related to the drug dose, duration of treatment, and degree of renal impairment. The clinical manifestations of systemic toxicity induced by the "old" tetracyclines and, apparently, minocycline, where the data are less straightforward,[17,21,22] include an elevated blood urea nitrogen, acidosis, anorexia, nausea, and vomiting. The resulting fluid loss contracts the extracellular fluid volume to further compromise renal function by reducing renal blood flow. A vicious cycle is induced, reversible with cessation of drug therapy, but which, if left unrecognized, may lead to excessive iatrogenic morbidity or death.

Doxycycline does not produce the metabolic effects described previously, and clinical data from a typical renal failure patient, reported by Little and Bailey,[23] well illustrate this point (Figure 7). In addition, doxycycline does not accumulate in renal failure for the reasons described earlier.

Fanconi syndrome. In 1963 Gross[24] and Frimpter et al.[25] described a reversible type of Fanconi syndrome (i.e., proximal tubular damage) induced by the use of outdated and degraded tetracyclines. They identified the major degradation products present in the outdated tetracycline capsules as anhydrotetracycline and epianhydrotetracycline. The subsequent animal studies by Benitz and Diermeier,[26] which evaluated the toxicity of three separate tetracycline degradation products (anhydrotetracycline, epitetracycline, and epianhydrotetracycline), indicate that epianhydrotetracycline is the most toxic of the degradation products. These derivatives of tetracycline develop only in hot, moist, acid conditions, and since citric acid is no longer used in the production of the tetracyclines it is unlikely that this complication of tetracycline administration will be noted again.

Distal tubular concentrating defect. That tetracycline can directly effect the renal tubules was first reported by Roth and colleagues[27] in 1967, when they demonstrated the development of a vasopressin-resistant form of nephrogenic diabetes insipidus associated with prolonged tetracycline therapy. Subsequently, demethylchlortetracycline has been noted to be by far the most effective tetracycline for the therapeutic production of a renal concentrating defect, such as might be clinically desired to manage resistant edema associated with inappropriate antidiuretic hormone secretion.[28-31] The diuretic action of demethylchlortetracycline is mediated by inhibition of both the production and the action of cyclic AMP on the distal concentrating and diluting segments of the nephron.[32] However, it is important to stress that the clinical toxicity of demethylchlortetracycline appears to outweigh totally its therapeutic effectiveness in water retention states, particularly in the setting of coexisting hepatic disease.[33]

Clinical Use in Simple and Complicated UTIs

Simple urinary tract infections are those infections detected in the absence of anatomic abnormalities in the renal parenchyma or urinary outflow tract, whereas complicated infections are those found in the clinical setting of upstream or downstream anatomic abnormalities. Because these

infections are considered in detail elsewhere in this symposium, only a few general remarks are included here.

Urinary tract infections. The antibiotic therapy of simple urinary tract infections is straightforward in that any one of several different antibiotics can be selected and the immediate clinical results will be similar. A sulfonamide, a penicillin analogue, a tetracycline, etc. are all reasonable selections. Physician preference and patient tolerance and compliance are perhaps the most important factors in selection, and drug dosage, duration of therapy, and follow-up management are reviewed elsewhere.[34]

It is worth reiterating that pregnant women should never receive tetracycline therapy because of the developmental hazards to the fetus and the propensity of pregnant women to develop tetracycline-induced hepatic toxicity.[35]

Complicated urinary tract infections. In the absence of renal functional impairment, any one of several antibiotics may be selected, but in this instance the isolated pathogen and its antimicrobial sensitivity profile become key factors in antibiotic selection. If renal impairment complicates the picture for tetracycline-sensitive organisms, the only reasonable drug in this category would appear to be doxycycline. In our investigation of humans with severe renal disease, we found low urine concentrations of doxycycline but remarkably effective renal tissue levels of the drug,[12] the latter probably reflecting the drug's previously noted lipophilicity. At the present time we are unable solidly to correlate measured renal tissue levels of an antimicrobial agent and clinical response to therapy.[10] This is a matter of continuing investigation.

SUMMARY

In treating patients with bacterial infection and preexisting renal disease a physician must exercise great care in the administration of any antibiotic chemotherapeutic compound. As a class, it has been customary in the past to recommend that all tetracyclines be avoided in renal failure. It is now apparent that doxycycline is an exception to the rule because it does not accumulate during renal insufficiency and it does not increase the preexisting level of blood urea nitrogen. In patients with severe renal disease, or in those already on maintenance dialysis, doxycycline can be administered safely by an oral or parenteral route in the usual therapeutic doses. It is then eliminated from the body by a nonrenal, nonhepatic, "alternate" gastrointestinal route of elimination. The other tetracyclines (i.e., oxytet-

racycline, tetracycline hydrochloride, etc.), used in such a clinical setting, will accumulate and aggravate prerenal azotemia because of their antianabolic biochemical action.

"Old" and degraded tetracyclines have previously been demonstrated to have direct toxic effects on the renal proximal tubule, but because of changes in manufacturing techniques this is no longer a real problem. Demethylchlortetracycline has important distal tubular actions, which promote the elimination of water in resistant edema states, but now appears to be too nephrotoxic for clinical purposes.

Tetracyclines are effective agents in the management of simple urinary tract infections. In the presence of preexisting renal disease complicated by renal infection, identification of the infecting organism and evaluation of its antibiotic sensitivity profile are the most important aids to drug selection. The clinical impact of the finding that doxycycline produces effective renal parenchymal drug concentrations in severely diseased human kidneys is currently under evaluation.

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